REMARKS

I. Status of the Claims

Claims 1-36 are pending in the application and stand rejected under 35 U.S.C. §112, first paragraph, 35 U.S.C. §112, second paragraph and 35 U.S.C. §103. The specific grounds for rejection, and applicants' response thereto, are set out in detail below.

II. Formalities

The examiner has pointed out minor errors in the specification and claims. These have been corrected by amendments provided above.

III. Rejection Under 35 U.S.C. §112, First Paragraph

The examiner has posed a number of rejections under §112, first paragraph, each of which are addressed below.

Claims 1-11 are rejected for the recitation of "increasing" the transcription of a constitutive promoter. The claims have been amended to delete any mention of increasing, thereby obviating the rejection. Claims 8 and 19 are rejected for the recitation of TIL's as a method of transfection. Applicants agree that TIL's are not a method of transfection and, on this basis alone, have amended the claims.

Claims 1-28 and 35 are rejected, apparently, on the grounds that gene therapy is believed, in general, to be non-enabling. Applicants respectfully traverse. It is submitted that the concerns described by Marshall, Wilson, Culver, Hodgson and Miller only tell one side of the story regarding gene therapy. While it must be acknowledged that gene therapy is not a trivial endeavor, it similarly must be recognized that the difficulties described by the references have not deterred the field. There are dozens of clinical trials in the U.S., and many more around the world, that involve the use of gene therapy. In reviewing this topic, it is not accurate to focus only on the technical hurdles faced by the field, and to ignore the successes.

For example, applicants specifically note the results of gene therapy in the treatment of severe combined immunodeficiency. Blaese *et al.* (1995) (attached). In this study, two children with a genetic defect in production of adenosine deaminase (ADA) were treated with a cloned ADA gene inserted into a retroviral vector. More than one year after this treatment both patients continued to show significant improvement in their immune system function. The results of gene therapy treatment were markedly superior to those produced earlier by alternative treatment means.

In a cancer therapy context, Roth *et al.* (1996) (attached) have shown that a recombinant retroviral vector targets tumor cells *in vivo*. Moreover, this vector, which encodes the tumor suppressor p53, provided a sufficient ***level*** of p53 expression that apoptosis, or programmed cell death, was triggered in these cells. The conclusion to be drawn from this trial is that retroviruses

not only can target cells *in vivo*, but they express sufficient levels of exogenous protein to affect the target cell's function. It is worth noting that the patients enrolled in this trial had failed standard therapies, again underlying the superiority of gene therapy.

Successful results with gene therapy are by no means limited to these examples. According to a recent review article, "Probably the most remarkable conclusion drawn from the human trials is that human gene transfer is indeed feasible ... [and] most studies have shown that genes can be transferred to humans whether the strategy is *ex vivo* or *in vivo*, and that all vector types function as intended. ***Taken together, the evidence is overwhelming, with successful human gene transfer having been demonstrated in 28 ex vivo and 10 in vivo studies***." R. Crystal (1995) (emphasis added; attached).

Turning to the instant specification, adenoviral vectors are disclosed at pages 10-13, liposomes are disclosed at pages 19-20, HSV vectors are disclosed at pages 20-21 and retroviruses are disclosed at page 21. At the time the priority application was filed, the skilled artisan was quite capable of manipulating these compositions and using them to transfer various genes, including those disclosed in the instant application, into host cells.

Moreover, the "enablement" requirement under §112, first paragraph, does not require that a therapy be approved by the FDA, much less provide a complete "cure." Rather, the specification need only show how to make and use the present invention. "We hold as we do

because it is our firm conviction that one who has taught the public that a compound exhibits some desirable pharmaceutical property in a standard experimental animal has made a significant and useful contribution to the art, even though it may eventually appear that the compound is without value in the treatment of humans." *In re Krimmel*, 130 USPQ 215, 219 (CCPA 1961).

In sum, applicants traverse this aspect of the rejection on the grounds that the record does not contain evidence or reasoning that the approaches set forth in the specification would not permit those of skill in the art to practice the invention as claimed. To the contrary, the action simply points to negative ***editorializing*** in the art with respect to targeting and gene delivery, and ignored more compelling ***evidence*** that the skilled artisan can target cells both *in vivo* and *ex vivo*.

Finally, the examiner rejects claims 1-30 and 35, allegedly because the claims are overly broad. Applicants traverse. It appears to be the examiner's position that claims directed to cytokines should be limited to TNF-α. Initially, applicants point out that most of the rejected claims do ***not*** recite cytokines. As to claim 12, which does recite cytokines generally, has been amended to recite TNF-α.

In light of the proffered amendments and comments, applicants respectfully request reconsideration and withdrawal of each of the preceding rejections.

IV. Rejections Under 35 U.S.C. §112, Second Paragraph

The examiner has raised a number of different issues under §112, second paragraph, each of which are addressed below:

Claims 1, 18 and 26 are rejected for alleged grammatical defects. Amendments have been provided.

Claim 1 is rejected for lacking a final step of achieving the goal of the preamble. The claims has been amended.

Claims 6, 14, 17, 25 and 28 are rejected as indefinite for a variety of reasons all relating to language in the Markush groups. Amendments are offered.

Claims 9 and 20 are rejected for the recitation "the liposome is DOTMA ...." The suggested amendment is provided.

Claims 12, 23 and 26 are rejected for the recitation of "secretes a cytokine in a mammalian cell ...." An amendment is provided that addresses the rejection.

Claims 13, 24 and 27 are rejected for appearing to have the entire vector construct under the control of the promoter. Amendments are provided to address the examiner's concerns.

Claims 18, 35 and 36 are rejected as lacking indication of expression and incomplete as lacking a final step whereby the preamble is satisfied. Amendments are provided.

V. Rejections Under 35 U.S.C. §103

The examiner has rejected all claims under §103 over Hallahan *et al.* (C15) or Hallahan *et al.* (C16), along with a variety of supporting references. The primary Hallahan *et al.* references are said to teach provision of TNF-α to cells, mice or humans, followed by the administration of ionizing radiation. The references are said to teach that this combined therapeutic approach results in enhanced effect of the radiation treatment. The references are acknowledged to be lacking in gene transfer methodology, for which the secondary references are cited (along with various other aspects of dependent claims). In sum, the examiner deems it obvious to transfer a TNF-α gene, as an exemplary radiosensitizing/radioprotective agent, into a cell or a cell of a patient for the purpose of an improved combined therapy approach for the treatment of cancer. Applicants respectfully traverse.

What the examiner is proposing, from both a legal and scientific standpoint, is that the provision of a polypeptide to a cell, animal or patient, is reasonably equivalent to the synthesis of

that same polypeptide within a cell or with a cell of an animal or a patient. The question first must be asked whether this assumption is valid, as a scientific matter. Then, having established what the skilled artisan would believe, it is necessary to determine whether that belief would satisfy the elements of a *prima facie* case of obviousness. Applicants submit, respectfully, that it would not.

Turning to the scientific issues, it is submitted that ***providing*** an exogenous polypeptide to a cell is a distinctly different phenomena that ***synthesizing*** an polypeptide encoded by an exogenous gene. When a polypeptide is provided, already synthesized, to a cell, there are several things that must take place before any meaningful result can take place. First, the polypeptide must either bind to a receptor on the surface of the cell. Perhaps, this will triggering an effect on the cell's metabolism via translation through a series of signaling events. Alternatively, the receptor binding could be followed by internalization of the polypeptide by the cell. Non-specific binding (*i.e.*, not receptor-mediated), followed by internalization, also may take place. In either one of these latter two scenarios, the importation of the polypeptide into the cell is likely to have dramatic effects on the very nature of polypeptide.

One of the primary methods for facilitating receptor-mediated uptake is via endosomal vesicles. In such a situation, receptors occupied by their cognate ligands usually migrate to a particular portion of the cell surface, where an invagination creates a vesicle with the ligand-bound receptors on the inside. These "endosome" then move through the cell until mating with a lysosome. Lysosomes are another form of intracellular vesicle. But these vesicles have very acidic

interiors and, following fusion with endosome, the contents of the endosome are drastically altered. At this point, the vesicle may deliver its contents to the cytoplasm or other subcellular compartment. A polypeptide, for example, likely would be cleaved into smaller fragments or, at a minimum, lose its natural conformation due to the low pH environment. In some cases, it is the protein fragment that has a particular activity, not the polypeptide as a whole. A similar series of events takes place during non-receptor mediated uptake. Thus, it should be clear that the polypeptide delivered to the cell cytoplasm is, very likely, vastly different from that which was original provided to the cell.

On the other hand, expression of a gene inside a cell is likely to provide a full length polypeptide, at least in the first instance. Because this polypeptide will not pass through the receptor-endosome-lysosome pathway, there is no way of knowing if the same sort of fragments will be produced. In addition, since the target cell may not normally produce the polypeptide, the typical post-translational modification of the polypeptides (cleavage of leader or "pro-" sequences, glycosylation, methylation, phosphorylation, esterification) may not take place. Finally, the polypeptide may be toxic when produced ***inside*** the cell, when it is not toxic when provided ***externally*** to the cell, or *vice versa*.

Thus, from a scientific standpoint, it is submitted that one cannot, without an empirical undertaking, know whether provision of a given polypeptide ***to*** a cell will be the same as expression of that same polypeptide ***within*** the cell. Because of this uncertainty, one of skill in the art would

not, *a priori*, expect that the results of Hallahan *et al.* (C15 & C16) would hold for transgene expression.

Applicants turn next to *In re O'Farrell*, 7 USPQ2d 1673 (Fed. Cir. 1988), which held that, in order for a reference or references to obviate an invention, it must be shown that the references contain (1) detailed enabling methodology for practicing the claimed invention; (2) a suggestion for modifying the prior art to practice the claimed invention; and (3) ***evidence suggesting that the invention would be successful***. It is submitted, in light of the above, that this could not be the case here.

In the more recent case of *In re Vaeck*, 20 USPQ2d 1438 (Fed. Cir. 1991), the Federal Circuit took the *O'Farrell* doctrine a step further. In *Vaeck*, the Federal Circuit stated that, in order for an examiner to make out a *prima facie* case of obviousness, at least two things must be shown. First, the prior art must have suggested, to those of ordinary skill in the art, that they should make the claimed composition. And second, the prior art must have demonstrated a reasonable expectation of success in practicing the invention. Again, it is submitted that, in light of the discussion above, such is not the case here.

Finally, it is worth noting the *O'Farrell* court's caution regarding the improper "obvious to try" standard. In the decision, it was stated that it is not appropriate for the PTO to inquire, pursuant to §103, as to "what was 'obvious to try' [in] ... explor[ing] a ... general approach that

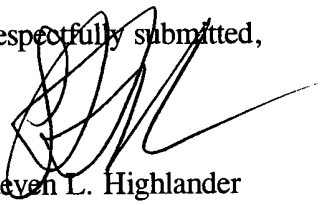
seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it." *O'Farrell* at 1681. Similarly, where the art provides merely "general guidance as to ... how to achieve" a particular goal, obviousness cannot be found. At best, the cited references merely present an "obvious to try" situation, and thus do not support a *prima facie* case.

Reconsideration and withdrawal of all the rejections under §103 is requested.

VI. Conclusion

In light of the foregoing amendments and remarks, applicants respectfully submit that all claims are in condition for allowance, and an early indication to that effect is solicited. Should Examiner Campell have any questions regarding this response, he is invited to contact the undersigned at the telephone number listed below.

Respectfully submitted,



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